ORIGINAL INVESTIGATION

Lack of Penicillin Resensitization in Patients With a History of Penicillin Allergy After Receiving Repeated Penicillin Courses

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Background: Up to 10% of the population reports an allergy to penicillin, yet more than 80% of these individuals lack penicillin-specific IgE antibodies. A negative result on a penicillin skin test is highly accurate in identifying who can safely receive the antibiotic at the time of testing. However, its negative predictive value for future courses is unknown because it is uncertain whether patients with a history of penicillin allergy are at risk of becoming resensitized.

Objective: To determine the rate of penicillin resensitization in adult patients with a history of penicillin allergy after they are challenged with repeated courses of oral penicillin.

Methods: Adult patients with a history of penicillin allergy consistent with an IgE-mediated mechanism were recruited and underwent penicillin skin testing. Those with negative skin test results were challenged with 3 successive 10-day courses of penicillin V potassium (250 mg by mouth 3 times a day), providing their penicillin skin test results remained negative prior to each course. Patients with positive skin test results were not challenged.

Results: Of 53 patients with initially negative skin test results, 46 completed the protocol, and each tolerated all 3 courses of penicillin with negative skin test results throughout. No patients had a converted skin test result from negative to a positive, yielding a resensitization rate of 0% (upper 95% confidence interval, 2.1%).

Conclusions: Adult patients with a history of penicillin allergy are not at increased risk of resensitization after receiving 3 courses of oral penicillin. Because a negative penicillin skin test result is predictive for subsequent oral administrations beyond the time of testing, adult patients with a history of penicillin allergy can be skin tested electively, which may avoid unnecessary treatment with alternate broad-spectrum antibiotics.

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PENICILLIN ALLERGY is the most commonly reported medication allergy. While up to 10% of patients report a history of penicillin allergy, numerous studies have shown that more than 80% of these patients lack penicillin-specific IgE antibodies and can receive the antibiotic safely.[1-5]

After the degradation products and immunogenic determinants of penicillin were elucidated in the 1960s,[6-8] penicillin skin testing became an accurate and valid method to detect the presence or absence of penicillin-specific IgE antibodies. Importantly, penicillin skin testing (when performed with major and minor determinants) has a very high negative predictive value of greater than 99% for immediate-type reactions.[3] When reactions have occurred in patients with negative skin test results who were given penicillin, they were mild and not life threatening[2-5]; penicillin-induced anaphylaxis has never been reported following a negative penicillin skin test result (using major and minor determinants).[9]

Although a negative penicillin skin test result is highly accurate in identifying who can safely receive the antibiotic at the time of testing, its negative predictive value for future courses of penicillin is not known.[10] There is a theoretical concern that some patients with a history of penicillin allergy may be resensitized by a course of penicillin, thus placing them at risk of developing an immediate allergic reaction if they were to take the antibiotic again. For this reason, the drug hypersensitivity practice parameter recommends that penicillin skin testing be repeated each time an adult patient with a history of penicillin allergy receives the antibiotic and that skin testing should be reserved for situations when there is an immediate need for penicillin.[10]

Some data indicate that the resensitization rate (conversion of a negative penicillin skin test result to a positive one) in children with a history of penicillin allergy after they are challenged with a single oral course of penicillin is low.[2,11] However, in the adult population, to our knowledge, there are no published reports ad-

SUBJECTS AND METHODS

Subjects were recruited among patients, staff, and students at University of Texas Southwestern Medical Center and affiliated institutions, Dallas. All portions of the study were approved by the University of Texas Southwestern Medical Center institutional review board. Inclusion criteria for patients were aged 18 years or older and history of an allergic reaction to penicillin consistent with an IgE-mediated mechanism. Exclusion criteria were pregnancy and use of β-blockers. Patients who were unable to recall their previous reaction and those who reported non–IgE-mediated type of reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) were excluded from participation. Likewise, patients who selectively had reacted only to amoxicillin or ampicillin (and not to penicillin) were not enrolled owing to to the possibility that their sensitivity was specific to a side chain rather than the β-lactam portion of the molecule, which has been reported previously.[14,15]

Qualifying patients underwent penicillin skin testing at the initial visit, and those who had negative skin test results were immediately challenged with a single oral dose of 250 mg of penicillin V potassium. Patients were observed for 30 minutes and then instructed to continue to take oral penicillin for 10 days (250 mg by mouth 3 times a day). Additional skin tests and challenges were performed in a similar manner outlined in **Figure 1**. Follow-up skin tests were performed at a minimum of 4 weeks after patients completed a given course of penicillin. Testing was not performed before this time because of the theoretical concern that skin testing sooner may result in a false-negative result due to patients being in a temporary desensitized state.[16] Patients whose skin test result remained negative received 3 courses of penicillin and underwent 4 penicillin skin tests. Patients with a positive skin test result at any point during the study would not be given further penicillin and therefore would be removed from the protocol.

Penicillin skin testing was carried out in typical fashion using major and minor determinants[10] The reagents used were 6×10^{-5}M penicilloyl-polylysine (Pre-Pen; Hollister-Stier Laboratories LLC, Spokane, Wash), 0.01M penicillin G sodium (Marsam Pharmaceuticals Inc, Cherry Hill, NJ), 0.01M penicilloic acid, 1M histamine, and normal saline solution. Penicilloic acid was prepared by alkaline hydrolysis of penicillin G, and its purity was analyzed by nuclear magnetic resonance, as has been described previously.[17] Briefly, using 0.1N sodium hydroxide, the pH of a penicillin G solution was adjusted to 12.0, at which it was maintained for 20 minutes and then adjusted back to 7.0 with 0.1N hydrochloric acid. Both penicilloic acid and penicillin G solutions were stored in single-use ampules, frozen, lyophilized, and reconstituted with normal saline solution immediately prior to skin testing.

All skin tests were performed in duplicate and were interpreted in the usual fashion outlined previously.[18,19] First, prick/puncture tests were performed with penicillin reagents and controls. A positive response was defined as a wheal of 3×3 mm or greater in diameter compared with negative control, measured 15 minutes after application. If prick test results with antigens were negative, intradermal tests were performed by injecting an amount (approximately 0.03 mL) sufficient to produce wheals measuring 4×4 mm in diameter. A positive response was defined as a wheal that increased at least 2×2 mm in diameter compared with negative control, measured 15 minutes after injection.

We sought to compare the resensitization rate in our patient sample with the 2% to 4% sensitization rate reported in the general population (hence, an average of 3%). Using a 1-proportion power analysis with a power level of 0.99 and an α level of .05, 99 follow-up penicillin skin tests (hence, 33 patients each underwent 3 follow-up skin tests after 3 oral penicillin challenges) were required to detect a 3% skin test conversion rate (from negative to positive). Statistical analysis was carried out using the binomial test with a 1-sided 95% confidence interval. We chose to treat the skin tests as independent observations because the probability of testing positive in a given subject was nondecreasing. The null hypothesis was that the proportion of patients who had converted skin test results would be greater than 3%.

dressing the issue of resensitization after oral penicillin. In addition, the risk of resensitization after more than 1 course of penicillin has not been evaluated in any patient population.

Our objective was to determine the rate of resensitization after repeated courses of oral penicillin are given to adult patients who have a convincing history of penicillin allergy but presently have a negative penicillin skin test result. Our hypothesis was that the rate of resensitization would not be higher than the 2% to 4% sensitization rate in the general nonallergic population.[3,4,12,13]

RESULTS

Characteristics of the enrolled patients are given in the **Table**. At the initial visit, 58 patients underwent penicillin skin testing. Five patients (9%) had positive skin test results and were not included in further analysis; 53 patients had negative results and thus were enrolled in the study. In the group with negative skin test results, 25 (47%) of the patients reported a history of urticaria or angioedema to penicillin, 9 (17%) had experienced anaphylaxis, and 19 (36%) had developed a pruritic rash. Approximately two thirds of the patients reported a history of atopy, and about a third reported a history of drug allergy to another medication in addition to penicillin. The mean length of time elapsed since a patient's previous reaction to penicillin was 25 years.

Of the 53 patients with negative skin test results, 46 completed the protocol. Each of these individuals tolerated all 3 courses of penicillin and had negative skin test results throughout (**Figure 2**). The 7 patients who withdrew from the study prior to completing the protocol are described below. Because no patients had a skin test result that converted from negative to positive, the resensitization rate was 0%. Applying the binomial test to the 142 skin tests following the penicillin courses (48 skin tests following the first course; 48 following the second course; and 46 following the third course), the 1-sided upper 95% confidence interval was 0.021 (or 2.1%), allowing us to reject the null hypothesis.

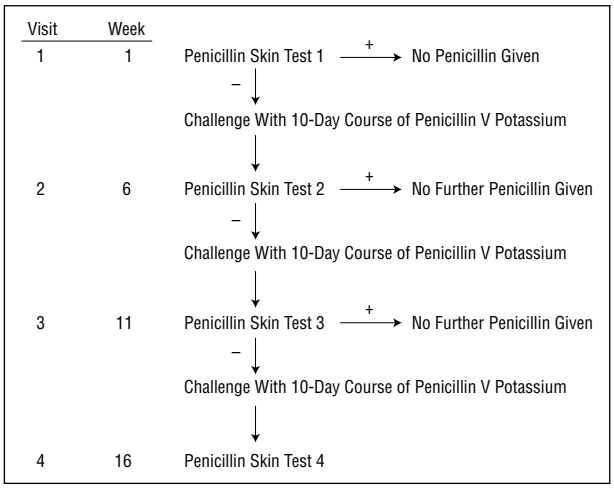

Figure 1. Algorithm of the study protocol. Penicillin skin testing at visits 2, 3, and 4 was performed at least 4 weeks following the conclusion of the previous course of penicillin. The plus sign indicates positive skin test result; the minus sign, negative skin test result.

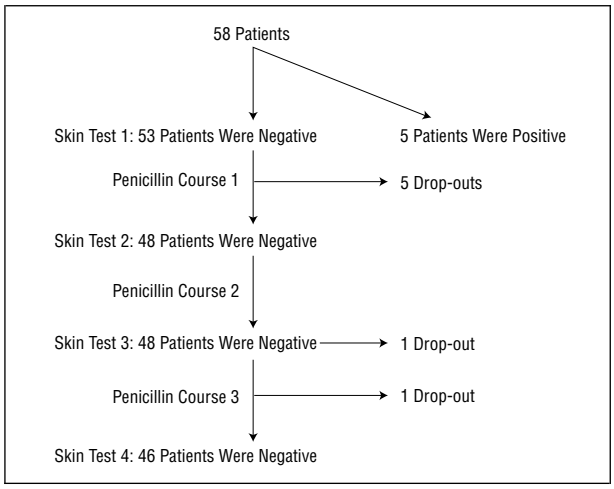

Figure 2. Summary of the results. None of 46 patients who completed the protocol had a converted penicillin skin test result from negative to positive.

Patient Characteristics*

Characteristic	Initial Negative Skin Test Result (n = 53)	Initial Positive Skin Test Result (n = 5)
Male/female sex	18 (34)/35 (66)	4 (80)/1 (20)
Mean age (range), y	39 (22-60)	27 (23-40)
Atopy	36 (68)	3 (60)
Other drug allergies	18 (34)	0
Family history of drug allergy	20 (38)	1 (20)
Reaction history		
Urticaria/angioedema	25 (47)	1 (20)
Pruritic eruption	19 (36)	2 (40)
Anaphylaxis	9 (17)	2 (40)
No. of years since reaction		
0-10	6 (11)	2 (40)
11-20	13 (25)	2 (40)
21-30	19 (36)	0
31-40	10 (19)	1 (20)
41-50	5 (9)	0
Mean No. of years since reaction (range)	25 (5-50)	16 (3-36)

*Data are number (percentage) of patients unless otherwise specified.

Of the 7 patients who withdrew from the study, 2 experienced adverse reactions that were possibly allergic in nature, but additional investigation revealed that they were not resensitized. The first patient developed pruritus limited to the groin on the second day of his first course of penicillin, which was not associated with a rash or any other symptoms. The second patient developed hives (by history, not visualized) on the 10th day of her second course of penicillin. Both of these patients had another penicillin skin test performed at least 4 weeks following their reactions, and both maintained negative skin test results (indicating they were not resensitized). Moreover, the second patient was challenged and tolerated a single full 250-mg oral dose of penicillin V potassium, further proving she had not developed penicillin-specific IgE antibodies. The first patient elected not to be challenged with penicillin. Both patients preferred not to continue the study. Because the first patient did not complete a single full course of penicillin, he was not included in the statistical analysis. The second patient was included in the analysis as having had 2 negative skin test results following the first 2 courses of penicillin before dropping out of the study (Figure 2).

The remaining 5 patients withdrew from the study because of relocation (2 patients), changed mind about participation (1 patient), vaginal yeast infection (1 patient), and noncompliance with follow-up (1 patient). Of these 5, 4 withdrew prior to the second penicillin skin test. One patient moved after she had tolerated all 3 courses of penicillin, but before her fourth skin test could be performed.

COMMENT

In this study, we have demonstrated for the first time that adult patients with a history of penicillin allergy but currently a negative penicillin skin test result are not at an increased risk of becoming resensitized by taking 3 oral courses of the antibiotic. Our results indicate that in adult patients with a history of penicillin allergy, a negative penicillin skin test result is predictive beyond the time of immediate administration and skin testing may not need to be repeated each time a patient requires treatment with the medication. A recent survey of practicing allergists highlighted the lack of a consensus opinion regarding the predictive value of penicillin skin testing and resensitization.[20] In this study, 32% of responder allergists stated that a negative penicillin skin test result is predictive only for immediate administration, 34% believed it to have no time limitation, while others found it predictive for periods ranging from 24 hours to 1 year.[20] Similarly, the percentage of allergists who would repeat penicillin skin testing in patients with a history of penicillin allergy who had since tolerated a course of penicillin ranged widely between 18% and 80%, depending on the patient's reaction history. The authors of the survey concluded that the observed variations in clinical practice were partially due to a lack of scientifically based information regarding penicillin resensitization.[20]

To our knowledge, penicillin resensitization after oral challenge has been studied only in pediatric patients with a history of penicillin allergy, following only a single course with the antibiotic. Mendelson et al[2] challenged children with a single 10-day course of penicillin V potassium and found a skin test conversion rate of 1.5%, while Pichichero et al,[11] using a similar protocol, found a resensitization rate of 14%. The latter study differed from the former in that some children were skin tested and challenged with β-lactams other than penicillin (including cephalosporins) and only included patients who had physician-documented reactions. In the adult population, there are 2 published reports, both of which evaluated resensitization after a single course with a parentally administered β-lactam antibiotic. Parker et al[21] studied a group of 18 patients, 3 (16%) of whom had a converted penicillin skin test result from negative to positive following a course with an intravenous β-lactam antibiotic. Lopez-Serrano et al[22] found a resensitization rate of 5% in adult patients after they were challenged with intramuscular penicillin (plus oral amoxicillin) over several days. Because the resensitization rate appears to be higher when adult patients are challenged parentally, it is possible that our results (using oral penicillin) cannot be generalized to patients who receive penicillin intravenously or intramuscularly.

Our study differs from previous investigations in several ways. First and most importantly, we challenged patients with repeated courses of penicillin rather than just a single course. This scenario better simulates real-life situations in which patients are likely to receive more than 1 antibiotic course over time. We believe that the design of our protocol was optimal to detect any possible resensitization because it is known that repeated exposure to a medication is more likely to produce sensitization in a previously nonallergic individual.[23]

Second, unlike previous investigations, we sought to only include patients who had reaction histories consistent with an IgE-mediated–type reaction because presumably these individuals would be the ones at highest risk of becoming resensitized. It is likely that among "all comers" labeled as having "penicillin allergy," there exist many patients erroneously labeled as "penicillin allergic." By taking a detailed history and reviewing medical records when possible, we attempted to minimize the possibility of including patients who had not previously experienced a penicillin-induced IgE-type reaction. Admittedly, because we relied on historical information, we cannot be certain that the patients' previous reactions were due to the presence of penicillin-specific IgE antibodies.

It could be argued that, ideally, one should prospectively follow penicillin-allergic patients and challenge them once their penicillin skin test results convert from positive to negative. Unfortunately, because it may take years or decades for patients to lose their penicillin sensitivity, such a prospective study would be difficult to perform.

A third difference between our study and others is that our protocol excluded patients who previously had reacted only to extended spectrum penicillins or cephalosporins (and not to penicillin itself). It is possible that some patients who experienced previous reactions to other β-lactams had a sensitivity to a side chain (that is specific to a particular compound), rather than to the common β-lactam component. The true allergy status of such patients cannot be accurately determined because skin testing with compounds other than penicillin determinants has not been validated and may produce false-positive or false-negative results.

One limitation to our study is that most enrolled patients had distant reaction histories. This selection bias was unintentional and probably due to the following factors: (1) considerable time is required for penicillin-allergic patients to lose their sensitivity, (2) patients with recent reactions and vivid memories of them may be less likely to consent to be challenged with penicillin, and (3) because the use of penicillin has declined in recent years in favor of extended-spectrum penicillins, cephalosporins, and other classes of antibiotics, fewer patients are being treated with (and hence reacting to) penicillin itself. We cannot determine if our results would have been different had most patients experienced recent, as opposed to distant, reactions. Nevertheless, among the group of 46 subjects who completed the protocol, none of the 6 patients who had experienced reactions within the last 10 years became resensitized.

Another potential limitation is that our subjects, unlike real-life clinical patients, were not sick at the time they received penicillin. Some non–IgE-mediated reactions to medications are known to occur with much higher frequency in the presence of certain concomitant viral infections; the 2 most notable examples are cutaneous eruptions secondary to ampicillin use in patients with Epstein-Barr virus and eruptions due to sulfamethoxazole use in patients with human immunodeficiency virus.[24,25] However, we are unaware of any descriptions of similar associations between infections and IgE-mediated reactions to medications. Additionally, in his clinical practice, one of us (H.E.) has repeated penicillin skin tests on several patients with a history of penicillin allergy in a manner similar to our protocol, the only difference being that these patients were ill and in need of a penicillin-class antibiotic. Some of these patients have been skin tested up to 5 times over a period of years, and none has become resensitized (unpublished data, 2000). Therefore, we believe it is unlikely that inclusion of sick patients in need of antibiotic treatment would have yielded different results.

It has been observed that physicians frequently choose to treat patients with a history of penicillin allergy with alternate broad-spectrum antibiotics.[26,27] The emergence of multiple drug-resistant bacteria in recent years is thought to be largely due to the unnecessary use of broad-spectrum antibiotics,[28-32] and the overall added cost to health care resulting from multiple drug–resistant organisms has been estimated to be over $4 billion annually.[33]

To help curtail the spread of multiple drug–resistant organisms, the Centers for Disease Control and Prevention and others have recommended more judicious use of broad-spectrum antibiotics.[29,34,35] One method to help achieve this goal would be for allergists to identify by penicillin skin testing the many adult patients labeled penicillin allergic who lack penicillin-specific IgE antibodies and who could receive penicillin-class antibiotics safely. Furthermore, because our data suggest that a single penicillin skin test is predictive not only for immediate administration but also for future courses with the antibiotic, skin testing may not need to be repeated each time a patient

with a history of penicillin allergy requires treatment. Rather, allergists could perform penicillin skin testing on an elective basis when the patient is well and not in need of antibiotic treatment. Because patients and physicians may not "trust" the negative result of a penicillin skin test (despite its very high negative predictive value), in clinical practice, an oral challenge with penicillin may be required to unequivocally prove its safety.

Unfortunately, the applicability of our results is somewhat limited by the fact that minor penicillin determinants (other than penicillin G) have yet to be approved by the Food and Drug Administration and therefore remain unavailable for widespread clinical use. Despite this fact, in a recent survey, over 40% of practicing allergists reported performing skin tests with minor determinants (which they presumably obtained from local medical centers).[20] Nonetheless, patients with a history of penicillin allergy can still be evaluated by allergists, and important and useful information can be obtained by skin testing solely with penicilloyl-polylysine and penicillin G.[10]

In summary, we have shown that adult patients who have lost their penicillin hypersensitivity are not at increased risk of becoming resensitized after taking repeated oral courses of the antibiotic. Our results extend the negative predictive value of penicillin skin testing beyond a single course and, hence, increase the usefulness of a single negative skin test result. Allergists can play a valuable role in clinical medicine by helping identify those patients labeled penicillin allergic who could receive penicillin-class antibiotics safely. In light of the increasing prevalence of multiple drug–resistant bacteria, rising cost of treatment, and recommendations to decrease the unnecessary use of broad-spectrum antibiotics, we believe that elective penicillin skin testing of adults with a history of penicillin allergy makes clinical and economic sense.

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There was no outside financial support for the project, but some complimentary samples of penicilloyl-polylysine (Pre-Pen) used in skin testing were provided to us by the manufacturer, Hollister-Stier, who was not involved in the design of the protocol, analysis of the data or any other phase of the project.

Preliminary findings from the project were presented orally in abstract form at the annual meeting of the American Academy of Allergy, Asthma and Immunology, San Diego, Calif, March 6, 2000.

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